

hydroxypropylcellulose, hydroxypropylmethylcellulose, and mixtures thereof,  
and

b) water or an alcohol-water mixture.

**Objection to the specification and rejection under 35 U.S.C. § 112**

The Examiner objected to amendments to paragraphs [010] and [022] of the specification made in the Amendment filed on September 20, 2005. The amendment to the specification deleted the words "one or more" in the phrase "one or more nonvolatile constituents" in both amended paragraphs. Applicants respectfully request that the Examiner withdraw the objection in view of the following comments.

As explained in the Amendment filed on September 20, 2005, the original disclosure conveys that urea and the hydrophilic film-forming agent are nonvolatile constituents in the context of this invention. An amendment to refer to "nonvolatile constituents, which comprise" urea and the hydrophilic film-forming agent is therefore supported in the specification. Indeed, it makes sense to delete reference to the phrase "one or more" simply because there are at least two nonvolatile constituents recited: urea and the hydrophilic film-forming agent.

The Examiner alleges that the original disclosure does not convey that urea and hydrophilic polymer are in fact non-volatile. With regard to urea in particular, the Examiner cites to the Merck Index as disclosing that urea can develop an odor of ammonia. The Examiner concludes that defining urea as non-volatile "goes against the chemistry of urea." Office Action at page 3. For this reason, the Examiner also rejects the claims as lacking written description support under 35 U.S.C. § 112, in addition to objecting to the specification.

Applicants disagree with the Examiner's analysis and conclusions. Paragraph [008] of the specification states that "the hydrophilic film-forming agent and urea are dissolved" in the water or water/alcohol mixture when the preparation is a solution. This disclosure supports the fact that water and the water/alcohol mixture are solvents of the solid, non-volatile, hydrophilic film-forming agent and urea. Further, after application of the solution an adherent film is formed on the nails, as discussed in paragraph [008].

Thus, water and alcohol evaporate, leaving the non-volatile constituents including the hydrophilic film-forming agent and urea in the film. These descriptions sufficiently differentiate between non-volatile constituents and volatile constituents used in the invention. Paragraph [036] of the specification furthermore describes an example where patients were treated with a preparation and the "urea-containing film which formed after the application to the nails was wipe-resistant and waterproof." This description of urea remaining within the applied film also conveys that urea is a non-volatile constituent in the preparations used according to the invention.

With respect to the alleged odor of urea developing into that of ammonia, applicants first point out that urea (chemical formula  $\text{CH}_4\text{N}_2\text{O}$ ) is a different compound from ammonia (chemical formula  $\text{NH}_3$ ). If urea "develops" an odor of ammonia, it appears that the urea is not pure or that it decomposes to give that odor. In this regard, applicants enclose a data sheet from the US Pharmacopeia (Attachment A), wherein it is stated that urea is "practically odorless," but may gradually develop a slight odor of ammonia upon "long standing." Applicants also enclose a further data sheet for urea (Attachment B), wherein under the category of "Inhalation Risk" it is stated that the evaporation of urea at 20 °C is "negligible." The data sheet also states that the melting point of urea is above 132 °C. This data supports a conclusion that urea is in fact a non-volatile constituent according to the present invention.

Lastly, the Examiner has simply confused an "odor" with volatility. Many solids, for example, have an odor but are not "volatile." Chocolate and cheddar cheese both have an odor but are not volatile. Nothing in the references cited by the Examiner supports the argument that urea is "volatile" in the context of this invention.

In view of the comments above, the objection to the specification and the rejection of the claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

### **Rejections under 35 U.S.C. § 102 and § 103**

The Examiner rejected claims 30 and 8-10 under 35 U.S.C. § 102(b) as being anticipated by GB 2 202 743 ("GB '743"). The Examiner also rejected claims 3-6 and 11-13 under 35 U.S.C. § 103(a) as being obvious in view of GB '743. In support of the rejections, the Examiner argued that GB '743 discloses a varnish formulation that

comprises urea in an amount of 41% by weight of the non-volatile constituents and EUDRAGIT, and that other claimed amounts of certain ingredients would have been obvious. See Example IV of GB '743. Applicants respectfully traverse these rejections.

GB '743, and in particular Example IV of that document, does not anticipate the pending claims. Urea does not appear to constitute 41% by weight of the non-volatile constituents in that Example as argued by the Examiner. The non-volatile constituents in Example IV are micronazole nitrate, urea, glycerol, and Eudragit E 100, which together are 26% by weight of the total composition. Urea is present in an amount of 10% by weight of the total composition and is, as a result, about 38.46% ( $=10/26$ ) by weight of the non-volatile constituents. The Examiner may have mistakenly identified glycerol as a volatile, rather than non-volatile, constituent in the preparation. The disclosure of glycerol as a plasticizer at page 5, line 7 of GB '743, however, makes clear that it is a non-volatile component.

As explained above, Example IV does not teach or suggest a preparation as claimed having urea present in an amount of from 41 percent by weight to 69 percent by weight, relative to the nonvolatile constituents of the preparation. The remainder of the disclosure similarly does not teach or suggest such an amount of urea. For at least this reason, the pending claims should be patentable over GB '743.

GB '743 also does not teach or suggest the presently-claimed method of hydrating brittle toenails or fingernails comprising applying the recited pharmaceutical preparation to brittle toenails or fingernails. Instead, the GB '743 disclosure relates to topical application of its preparation in the treatment of fungal infections of the nails or surrounding tissues. GB '743 does not inherently or explicitly refer to application of its preparation to brittle toenails or fingernails and for at least this reason does not teach or suggest the claimed invention.

Moreover, the EUDRAGIT cited by the Examiner at 12 weight percent of the total composition (disclosed in Example IV Varnish on page 6 of GB '743) does not fall within the meaning of the hydrophilic film-forming agent recited in claim 30. Applicants enclose a data sheet for Eudragit E 100 (Attachment C), which is a copolymer of dimethylaminoethyl methacrylate and neutral methacrylic esters. Eudragit E 100 is

disclosed as being "practically insoluble" in water. See "Solubility," page 2 of 4. On the other hand, the pharmaceutical preparation that is applied to brittle toenails or fingernails in the method of the present invention is in the form of a solution.

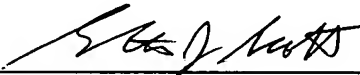
For at least the reasons provided above, the pending claims should be patentable in view of GB '743.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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GARRETT & DUNNER, L.L.P.

Dated: November 21, 2006

By:   
Steven J. Scott  
Reg. No. 43,911

# ATTACHMENT A

- My USP-NF
- Bookmarks
- Searches
- USP29-NF24 :
  - Front Matte
  - General No
  - Notice of R
  - USP Mono
  - Dietary Sup
  - General Ch
  - Dietary Sup
  - Reagents
    - Reagent
    - Reagent
    - Indicator
    - Solution
  - Reference
  - NF Monogr
  - Chromatog
  - Appendices
  - Glossary
- Contact USP
  - USP Home
  - Technical S
  - Email Softv
  - Email Cust



**Ubidecarenone:** Yellow to orange, crystalline powder. Melts at about 48°. Soluble in ether; very slightly soluble in dehydrated alcohol; practically insoluble in water.

**Undecylenic Acid:** Clear, colorless to pale yellow liquid having a characteristic odor. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils.

**Urea :** Colorless to white, prismatic crystals, or white, crystalline powder, or small white pellets. Is practically odorless, but may gradually develop a slight odor of ammonia upon long standing. Its solutions are neutral to litmus. Freely soluble in water and in boiling alcohol; practically insoluble in chloroform and in ether.

**Ursodiol:** White or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether.

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# **ATTACHMENT B**



<b>UREA</b>		<b>ICSC: 0595</b>	
<b>Date of peer-review: October 1997</b> Carbamide Carbonyldiamide			
CAS #	57-13-6	NH <sub>2</sub> CONH <sub>2</sub> / CH <sub>4</sub> N <sub>2</sub> O	
RTECS #	YR6250000	Molecular mass: 60.1	
UN #			
EC #			
<b>TYPES OF HAZARD / EXPOSURE</b>	<b>ACUTE HAZARDS / SYMPTOMS</b>	<b>PREVENTION</b>	<b>FIRST AID / FIRE FIGHTING</b>
<b>FIRE</b>	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: all extinguishing agents allowed.
<b>EXPLOSION</b>			
<b>EXPOSURE</b>		<b>PREVENT DISPERSION OF DUST!</b>	
<b>Inhalation</b>	Cough. Shortness of breath. Sore throat.	Local exhaust.	Fresh air, rest.
<b>Skin</b>	Redness.	Protective gloves.	Rinse and then wash skin with water and soap.
<b>Eyes</b>	Redness.	Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
<b>Ingestion</b>	Convulsions. Headache. Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Give plenty of water to drink. Rest.
<b>SPILLAGE DISPOSAL</b>		<b>PACKAGING &amp; LABELLING</b>	
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Wash away remainder with plenty of water.		<b>EU Classification</b> <b>UN Classification</b>	
<b>EMERGENCY RESPONSE</b>		<b>STORAGE</b>	
		Separated from incompatible materials, (see chemical dangers).	
<b>IPCS</b> International Programme on		Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities © IPCS, CEC 2001	



Chemical Safety

SEE IMPORTANT INFORMATION ON  
BACK

UREA

ICSC: 0595

## IMPORTANT DATA

**PHYSICAL STATE; APPEARANCE:**WHITE CRYSTALS, WITH CHARACTERISTIC  
ODOUR.**CHEMICAL DANGERS:**The substance decomposes on heating above melting  
point producing toxic gases. Reacts violently with  
strong oxidants, nitrites, inorganic chlorides, chlorites  
and perchlorates causing fire and explosion hazard.**OCCUPATIONAL EXPOSURE LIMITS:**

TLV not established.

**ROUTES OF EXPOSURE:**The substance can be absorbed into the body by  
inhalation of its aerosol and by ingestion.**INHALATION RISK:**Evaporation at 20°C is negligible; a nuisance-causing  
concentration of airborne particles can, however, be  
reached quickly if powdered.**EFFECTS OF SHORT-TERM EXPOSURE:**The substance irritates the eyes, the skin and the  
respiratory tract.**EFFECTS OF LONG-TERM OR REPEATED  
EXPOSURE:**Repeated or prolonged contact with skin may cause  
dermatitis.

## PHYSICAL PROPERTIES

Melting point: 132.7-135°C

Density: 1.32

Solubility in water: miscible

Octanol/water partition coefficient as log Pow: -3.00 to  
-1.54

## ENVIRONMENTAL DATA

## NOTES

Temperature of decomposition unknown in literature.

## ADDITIONAL INFORMATION

**LEGAL NOTICE**Neither the CEC nor the IPCS nor any person acting on behalf of the CEC or the IPCS  
is responsible for the use which might be made of this information

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See Also:

Toxicological AbbreviationsUrea (WHO Food Additives Series 32)UREA (JECFA Evaluation)Urea (SIDS)

# **ATTACHMENT C**

Specification

**Specifications and test methods for  
EUDRAGIT® E 100, EUDRAGIT® E PO and EUDRAGIT® E 12,5**

"Basic butylated methacrylate copolymer" Ph. Eur.  
"Aminoalkyl Methacrylate Copolymer E" JPE

**1 Commercial form**

**EUDRAGIT® E 100**

Solid substance. EUDRAGIT® E 100 is described in the monographs quoted above.

**EUDRAGIT® E PO**

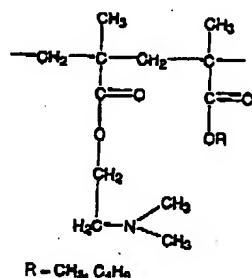
Solid substance obtained from EUDRAGIT® E 100. EUDRAGIT® E PO is described in the monographs quoted above.

**EUDRAGIT® E 12,5**

Solution of EUDRAGIT® E 100 with 12.5 % (w/w) dry substance in a mixture of 60 % (w/w) Isopropyl Alcohol Ph. Eur. / USP and 40 % (w/w) Acetone Ph. Eur. / NF.

**2 Chemical structure**

EUDRAGIT® E 100 is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters.



The average molecular weight is approx. 150,000.

**3 Characters**

**Description**

EUDRAGIT® E 100: colourless to yellow tinged granules with a characteristic amine-like odour.  
EUDRAGIT® E PO: white powder with a characteristic amine-like odour.

EUDRAGIT® E 12,5: light yellow liquid of low viscosity, clear to slightly cloudy. The odour is characteristic of the solvents.

#### **Solubility**

1 g of EUDRAGIT® E 100 or EUDRAGIT® E PO dissolves in 7 g methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride or 1 N hydrochloric acid to give clear to slightly cloudy solutions. EUDRAGIT® E 12,5 is mixable with these solvents and with petroleum ether in a ratio of 1:1.

The solid substance is practically insoluble in petroleum ether and water. The polymer is precipitated from EUDRAGIT® E 12,5 when mixed with water in a ratio of 1:1.

#### **4 Tests**

##### **Test solution**

Either EUDRAGIT® E 12,5 is used for the Test solution, or a corresponding solution of EUDRAGIT® E 100 or EUDRAGIT® E PO: 12.5 % (w/w) dry substance is dissolved in a mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

##### **Particle size**

EUDRAGIT® E PO: At least 90 % < 0.315 mm according to Ph. Eur. 2.1.4 or USP <811>.

##### **Film formation**

When the Test solution is poured onto a glass plate, a clear film forms upon evaporation of the solvents.

##### **Dry substance / Residue on evaporation**

EUDRAGIT® E 100 / EUDRAGIT® E PO : not less than 98.0 %. 1 g is dried in an oven for 3 hrs at 110 °C, according to Ph. Eur. 2.2.32 d.

EUDRAGIT® E 12,5: 11.9 - 13.1 %. 20 g quartz sand are mixed with 1 g of the solution and dried in an oven for 5 hrs at 110 °C, according to Ph. Eur. 2.2.32 d.

##### **Loss on drying**

EUDRAGIT® E 100 / EUDRAGIT® E PO: max. 2.0 % according to "Dry substance / Residue on evaporation."

##### **Assay**

EUDRAGIT® E 100 / EUDRAGIT® E PO / EUDRAGIT® E 12,5:  
20.8 - 25.5 % dimethylaminoethyl (DMAE) groups on dry substance (DS)

Alkali value: 162 – 198 mg KOH per g DS

*The alkali value (AV) is defined similarly to the acid value. It states how many mg KOH are equivalent to the basic groups contained in 1 g dry substance (DS).*

The assay is performed according to Ph. Eur. 2.2.20 "Potentiometric titration" or USP <541>. 0.2 g EUDRAGIT® E 100 / EUDRAGIT® E PO or 1.6 g EUDRAGIT® E 12,5 are dissolved in 96 ml glacial acetic acid and 4 ml water. 0.1 N perchloric acid is used as the titrant.

$$AV \text{ (mg KOH / g DS)} = \frac{\text{ml 0.1 N HClO}_4 \cdot 561}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

$$\text{DMAE groups (\%)} = AV \text{ (mg KOH / g DS)} \cdot 0.1286$$

EUDRAGIT® E 100 / EUDRAGIT® E PO : 4.0 - 6.0 % Nitrogen on dry substance according to JPE.

## **Colour**

Absorbance (A): max. 0.300. The yellow colour of the test solution is determined against water at 420 nm in a 1 cm cuvette, according to Ph. Eur. 2.2.25.

## **Viscosity / Apparent viscosity**

EUDRAGIT® E 100 / EUDRAGIT® E PO / EUDRAGIT® E 12,5: 3 - 6 mPa · s

The viscosity of the Test solution is determined by means of a Brookfield viscometer (UL adapter / 30 rpm / 20 °C).

EUDRAGIT® E 100 / EUDRAGIT® E PO: 2.5 - 5.5 mm<sup>2</sup> / s according to JPE.

## **Refractive index**

$n_D^{20}$ : 1.380 - 1.385. The refractive index of the Test solution is determined according to Ph. Eur. 2.2.6.

## **Relative density**

$d_{20}^{20}$ : 0.811 - 0.821. The relative density of the Test solution is determined according to Ph. Eur. 2.2.5.

## **5 Purity**

### **Sulphated ash / Residue on ignition**

Max. 0.1 % according to Ph. Eur. 2.4.14 or USP <281>.

1 g EUDRAGIT® E 100 or EUDRAGIT® E PO or EUDRAGIT® E 12,5 is used for the test.

### **Heavy metals**

Max. 20 ppm according to Ph. Eur. 2.4.8 method C or USP <231> method II.

1 g EUDRAGIT® E 100 or EUDRAGIT® E PO or EUDRAGIT® E 12,5 is used for the test.

### **Arsenic**

Max. 2 ppm according to JP Method 3, Apparatus B.

1.0 g EUDRAGIT® E 100 or EUDRAGIT® E PO or EUDRAGIT® E 12,5 is used for the test.

### **Monomers**

EUDRAGIT® E 100 / EUDRAGIT® E PO: < 3000 ppm

Butyl methacrylate: < 1000 ppm

Methyl methacrylate: < 1000 ppm

Dimethylaminoethyl methacrylate: < 1000 ppm

EUDRAGIT® E 12,5: total of monomers max. 0.04 %

The test is performed according to the Ph. Eur. monograph on 1 g EUDRAGIT® E 100 or 1 g EUDRAGIT® E PO or 8 g EUDRAGIT® E 12,5.

### **Microbial count**

Max. 1,000 CFU / g; Salmonella not detectable in 10 g; E. coli, S. aureus, Ps. aeruginosa not detectable in 1 g. The test is performed according to Ph. Eur. 2.6.12 and 2.6.13.

## **6 Identity testing**

### **First identification**

The material must comply with the tests for "Assay" and "Viscosity / Apparent viscosity."

### **Second identification**

IR spectroscopy on a dry film approx. 15 µm thick. To obtain the film, a few drops of the Test solution are placed on a crystal disc (KBr, NaCl) and dried in vacuo for about 2 hours at 70 °C.

The figure on page 4 shows the characteristic bands of the ester groups at 1,150 - 1,190, 1,240 and 1,270  $\text{cm}^{-1}$ , as well as the C = O ester vibration at 1,730  $\text{cm}^{-1}$ . In addition,  $\text{CH}_x$  vibrations can be discerned at 1,385, 1,450 - 1,490 and 2,950  $\text{cm}^{-1}$ . The absorptions at 2,770 and 2,820  $\text{cm}^{-1}$  can be assigned to the dimethylamino groups.

## 7 Detection in dosage forms

The dosage forms are extracted using the solvents listed under "Solubility," if necessary after crushing. Insoluble substances are isolated by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by IR spectroscopy.

## 8 Storage

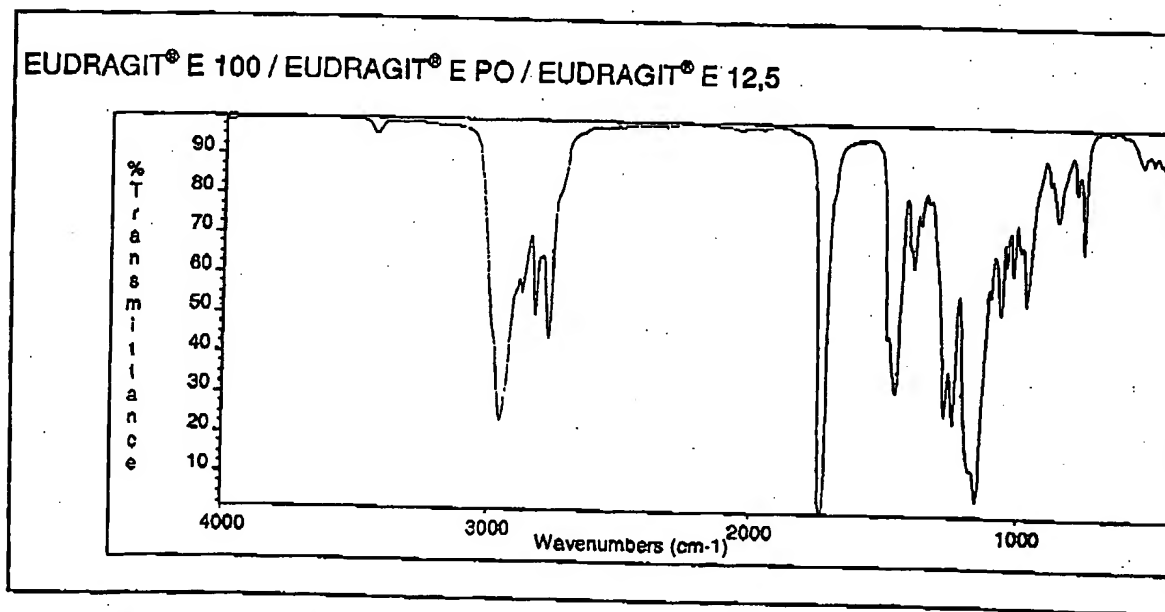
Protect from warm temperatures (USP, General Notices).  
Protect EUDRAGIT® E 100 and EUDRAGIT® E PO from moisture.  
Keep EUDRAGIT® E 12,5 in tightly closed containers.

EUDRAGIT® E 100 tends to form lumps at warm temperatures. This has no influence on the quality. The lumps are easily broken up again.

Temperatures above 25 °C will cause caking of EUDRAGIT® E PO. The product must therefore be stored well closed at or below room temperature.

## 9 Stability

Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage Stability data are available upon request.



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